Vascular Medicine

Diesel Exhaust Inhalation Causes Vascular Dysfunction and Impaired Endogenous Fibrinolysis

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Background—Although the mechanisms are unknown, it has been suggested that transient exposure to traffic-derived air pollution may be a trigger for acute myocardial infarction. The study aim was to investigate the effects of diesel exhaust inhalation on vascular and endothelial function in humans.

Methods and Results—In a double-blind, randomized, cross-over study, 30 healthy men were exposed to diluted diesel exhaust (300 μg/m^3 particulate concentration) or air for 1 hour during intermittent exercise. Bilateral forearm blood flow and inflammatory factors were measured before and during unilateral intrabrachial bradykinin (100 to 1000 pmol/min), acetylcholine (5 to 20 μg/min), sodium nitroprusside (2 to 8 μg/min), and verapamil (10 to 100 μg/min) infusions 2 and 6 hours after exposure. There were no differences in resting forearm blood flow or inflammatory markers after exposure to diesel exhaust or air. Although there was a dose-dependent increase in blood flow with each vasodilator ($P<0.0001$ for all), this response was attenuated with bradykinin ($P<0.05$), acetylcholine ($P<0.05$), and sodium nitroprusside ($P<0.001$) infusions 2 hours after exposure to diesel exhaust, which persisted at 6 hours. Bradykinin caused a dose-dependent increase in plasma tissue plasminogen activator ($P<0.0001$) that was suppressed 6 hours after exposure to diesel ($P<0.001$; area under the curve decreased by 34%).

Conclusions—At levels encountered in an urban environment, inhalation of dilute diesel exhaust impairs 2 important and complementary aspects of vascular function in humans: the regulation of vascular tone and endogenous fibrinolysis. These important findings provide a potential mechanism that links air pollution to the pathogenesis of atherothrombosis and acute myocardial infarction. (***Circulation***. 2005;112:3930-3936.)

Key Words: air pollution ∎ endothelium ∎ blood flow ∎ fibrinolysis

Air pollution is a major cause of cardiovascular morbidity and mortality. Short-term increases in air pollution exacerbate cardiorespiratory disease, leading to hospitalization for conditions including acute myocardial infarction.[1] Long-term repeated exposure increases the risk of cardiovascular mortality, with deaths attributable to ischemic heart disease, arrhythmias, and heart failure.[2] These associations are strongest for fine particulate air pollutants (PM$_{2.5}$),[3] of which the combustion-derived nanoparticulates of diesel exhaust are an important component.[4] Although significant improvements in air quality have occurred during the last 50 years, the association between PM$_{2.5}$ and mortality is evident below current air quality standards.[5]

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Despite the strength of the epidemiological evidence and the emergence of promising hypotheses,[6,7] the important constituents and biological mechanisms responsible for the cardiovascular effects of air pollution are largely unknown. It was recently reported that transient exposure to road traffic may increase the risk of acute myocardial infarction.[8] Long-term exposure to traffic in those living within 100 m of a major road significantly increased cardiopulmonary mortality.[9] These important observations suggest that the combustion-derived particulates in PM$_{2.5}$ may be critical in determining the cardiovascular effects of air pollution.

Abnormal endothelial function has been widely recognized in patients with atherosclerosis and its risk factors.[10,11] Endothelial dysfunction can also predict the likelihood of future cardiovascular events and death in patients with coronary artery disease[12] and in at-risk individuals with normal coronary arteries.[13] We have previously demonstrated endothelial dysfunction in both the peripheral and coronary circulations

of cigarette smokers.[10,11] Given the potential for common etiologic factors contained within polluted air and cigarette smoke, we hypothesized that the adverse cardiovascular effects of air pollution are a result of combustion-derived particulates and are mediated by an impairment of normal vascular function. Using a carefully characterized exposure system, we sought to assess the effect of diluted diesel exhaust inhalation on endothelial vasomotor and fibrinolytic function in humans.

Methods

Subjects

Thirty healthy, male nonsmokers between 20 and 38 years old participated in these studies, which were performed with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki, and the written, informed consent of all volunteers. Subjects taking regular medication and those with clinical evidence of atherosclerotic vascular disease, arrhythmias, diabetes mellitus, hypertension, renal or hepatic failure, asthma, significant occupational exposure to air pollution, or an intercurrent illness likely to be associated with inflammation were excluded from the study. Subjects had normal lung function and reported no symptoms of respiratory tract infection for at least 6 weeks before or during the study.

Study Design

Subjects attended the experimental sessions on 2 occasions 2 weeks apart and received either filtered air or diesel exhaust in a randomized, double-blind, cross-over design. Each subject was exposed for 1 hour in a specially built diesel exposure chamber according to a previously described standard protocol.[14] During each exposure, they performed moderate exercise (minute ventilation, $25 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) on a bicycle ergometer that was alternated with rest at 15-minute intervals.

Based on previous exposure[15] and systemic inflammatory[16] studies, vascular assessments were performed in 15 subjects at 6 to 8 hours after diesel or air exposure. In light of our findings from this 6- to 8-hour study, we subsequently determined vascular function in another 15 subjects at an earlier time point of 2 to 4 hours after exposure to diesel exhaust or air. All subjects abstained from alcohol for 24 hours and from food, tobacco, and caffeine-containing drinks for at least 4 hours before each vascular study. Studies were carried out in a quiet, temperature-controlled room maintained at 22°C to 24°C with subjects lying supine. All subjects remained indoors between the exposure and vascular assessment to minimize additional exposure to particulate air pollution.

Diesel Exposure

The diesel exhaust was generated from an idling Volvo diesel engine (Volvo TD45, 4.5 L, 4 cylinders, 680 rpm) as described previously.[15] More than 90% of the exhaust was shunted away, and the remaining part was diluted with air and fed into the exposure chamber at a steady-state concentration. The air in the exposure chamber was continuously monitored for nitrogen oxides (NO, NO_2), carbon monoxide (CO), particulates (number/cm³), and total hydrocarbons. The exposures were standardized by keeping the particulate concentration at 300 $\mu g/m^3$ and were associated with concentrations of NO_2 of 1.6 ppm; of NO, 4.5 ppm; of CO, 7.5 ppm; of total hydrocarbons, 4.3 ppm; of formaldehyde, 0.26 $\mu g/m^3$; and of suspended particles, $1.2 \times 10^6/cm^3$. The temperature and humidity in the chamber were controlled at 20°C and 50%, respectively.

Vascular Studies

All subjects underwent brachial artery cannulation with a 27-standard wire gauge steel needle under controlled conditions. After a 30-minute baseline saline infusion, acetylcholine at 5, 10, and 20 $\mu g/min$ (endothelium-dependent vasodilator that does not release

tissue plasminogen activator [t-PA]; Merck Biosciences); bradykinin at 100, 300, and 1000 pmol/min (endothelium-dependent vasodilator that releases t-PA; Merck Biosciences); and sodium nitroprusside at 2, 4, and 8 $\mu g/min$ (endothelium-independent vasodilator that does not release t-PA; David Bull Laboratories) were infused for 6 minutes at each dose. The 3 vasodilators were separated by 20-minute saline infusions and given in a randomized order. In the second cohort with the early (2- to 4-hour) vascular assessment, verapamil at 10, 30, and 100 $\mu g/min$ (endothelium- and NO-independent vasodilator that does not release t-PA) was infused at the end of the study protocol.[17]

Forearm blood flow (FBF) was measured in infused and noninfused arms by venous occlusion plethysmography with a mercury-in–silicone elastomer strain gauges as described previously.[18] Supine heart rate and blood pressure in the noninfused arm were monitored at intervals throughout each study with a semiautomated, noninvasive, oscillometric sphygmomanometer.

Venous cannulas (17 gauge) were inserted into large subcutaneous veins of the antecubital fossae of both arms. Blood (10 mL) was withdrawn simultaneously from each arm at baseline and during infusion of each dose of bradykinin and collected into acidified buffered citrate (Stabilyte tubes, Biopool International) for t-PA assays and into citrate (BD Vacutainer) for plasminogen activator inhibitor type 1 (PAI-1) assays. Samples were kept on ice before being centrifuged at 2000g for 30 minutes at 4°C. Platelet-free plasma was decanted and stored at −80°C before assay. Plasma t-PA and PAI-1 antigen concentrations were determined by ELISAs (TintElize t-PA, Biopool EIA; Coaliza PAI-1, Chromogenix AB). Hematocrit was determined by capillary tube centrifugation at baseline and during infusion of bradykinin at 1000 pmol/min.

Blood samples were taken immediately before and at 2 and 6 hours after exposure and analyzed for total cells, differential cell counts, and platelets by an autoanalyzer. Plasma interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured with commercially available ELISAs (Quantikine, R&D Systems). Plasma immunoreactive big endothelin (ET)-1 and ET-1 concentrations were measured according to an acetic acid extraction technique by use of a modified commercial radioimmunoassay with rabbit anti-human big ET-1 or ET-1 (Peninsula Laboratories Europe), as described previously.[19] Serum C-reactive protein (CRP) concentrations were measured with an immunonephelometric assay (Behring BN II nephelometer).

Data Analysis and Statistics

Plethysmographic data were analyzed as described previously.[10] The estimated net release of t-PA antigen was defined as the product of the infused forearm plasma flow (based on the mean hematocrit and the infused FBF) and the concentration difference between the infused and noninfused arms.[10] Continuous variables are reported as mean±SEM. Statistical analyses were performed with GraphPad Prism (Graph Pad Software) by ANOVA with repeated measures and 2-tailed Student t test, where appropriate. The area under the curve was calculated for the estimated net release of t-PA during the forearm study period. Statistical significance was taken at $P<0.05$.

Results

There were no differences in resting heart rate, blood pressure, or baseline FBF after exposure to diesel exhaust or air in either cohort (Table 1). Leukocyte, neutrophil, and platelet counts; plasma IL-6, TNF-α, big ET-1, and ET-1; and serum CRP concentrations were not altered by diesel or air exposure (Table 2).

Bradykinin, acetylcholine, and sodium nitroprusside caused dose-dependent increases in FBF after both air and diesel exhaust exposure ($P<0.0001$; Figure 1). The increase in blood flow was blunted 2 hours after exposure to diesel exhaust in response to infusion of bradykinin ($P<0.05$), acetylcholine ($P<0.05$), and sodium nitroprusside ($P<0.001$), and this dimin-

TABLE 1.   Baseline Hemodynamics Variables

	Air	Diesel	Significance
2 Hours, n=15			
Heart rate, bpm	64±3	65±2	$P=0.64$
Systolic blood pressure, mm Hg	140±4	148±4	$P=0.13$
Diastolic blood pressure, mm Hg	71±3	77±4	$P=0.08$
Infused FBF, mL/100 mL tissue per min	3.3±0.6	3.1±0.4	$P=0.45$
Noninfused FBF, mL/100 mL tissue per min	2.3±0.2	2.6±0.4	$P=0.30$
6 Hours, n=15			
Heart rate, bpm	61±2	60±2	$P=0.66$
Systolic blood pressure, mm Hg	138±5	138±3	$P=0.39$
Diastolic blood pressure, mm Hg	75±2	76±4	$P=0.87$
Infused FBF, mL/100 mL tissue per min	3.1±0.5	2.5±0.2	$P=0.25$
Noninfused FBF, mL/100 mL tissue per min	2.2±0.1	2.4±0.3	$P=0.65$

Values are reported as mean±SEM, 2-tailed paired *t* test.

ished response persisted at 6 hours (Figure 2). In contrast, verapamil-induced vasodilatation was unaffected after exposure to air or diesel exhaust (*P*=NS).

Bradykinin caused a dose-dependent increase in plasma t-PA antigen concentrations (*P*<0.0001; Table 3) that was reduced 6 hours after diesel exposure (*P*<0.001). The estimated net t-PA antigen release was reduced by 34% 6 hours after exposure to diesel (*P*<0.05; Figure 3) but was unaffected at the earlier time point of 2 hours.

TABLE 2.   Systemic Effects of Exposure to Diesel Exhaust

|	Before Exposure	2 Hours	6 Hours
Air			
Leucocytes, $\times10^9$ cells/L	5.1±0.2	5.6±0.3	5.3±0.3
Neutrophils, $\times10^9$ cells/L	2.8±0.2	3.3±0.2	3.0±0.2
Platelets, $\times10^9$ cells/L	217±12	216±9	218±12
IL-6, pg/mL	2.6±1.3	...	3.4±0.8
TNF-α, pg/mL	16.9±1.1	...	17.8±1.2
CRP, mg/L	0.9±0.3	...	0.8±0.2
PAI-1 antigen, ng/mL	20.2±3.9	19.2±2.8	18.5±3.7
t-PA antigen, ng/mL	6.6±0.6	7.0±0.6	6.0±0.5
ET-1, pg/mL	4.9±0.5	4.9±0.5	4.9±0.4
Big ET-1, pg/mL	28.8±1.5	29.6±2.5	32.2±2.5
Diesel			
Leucocytes, $\times10^9$ cells/L	5.6±0.3	5.7±0.4	5.1±0.3
Neutrophils, $\times10^9$ cells/L	2.8±0.2	3.4±0.3	2.9±0.3
Platelets, $\times10^9$ cells/L	228±14	227±11	221±12
IL-6, pg/mL	2.7±0.7	...	4.3±2.2
TNF-α, pg/mL	15.3±0.5	...	16.0±0.8
CRP, mg/L	1.0±0.4	...	0.7±0.4
PAI-1 antigen, ng/mL	16.1±3.0	15.7±3.6	12.8±2.6
t-PA antigen, ng/mL	6.0±0.6	5.9±0.6	5.3±0.6
ET-1, pg/mL	4.5±0.4	4.8±0.3	4.8±0.5
Big ET-1, pg/mL	30.2±2.3	31.9±3.7	28.1±2.6

Values are reported as mean±SEM.

Discussion

This is the first study to demonstrate that inhalation of diesel exhaust, a common urban air pollutant, can impair vascular function in humans. Using a robust and powerful study design, we have assessed 2 important and complementary aspects of vascular function: the regulation of vascular tone and endogenous fibrinolysis. Both are impaired and plausibly related to the well-documented cardiovascular effects of air pollution. These important findings provide a plausible mechanism that links air pollution to the pathogenesis of atherothrombosis and acute myocardial infarction.

Vasomotor Function

Impaired endothelium-dependent and -independent vasomotor function in the forearm vascular bed is associated with an increased risk of acute cardiovascular events, including cardiac death.[12] We have demonstrated that inhalation of diesel exhaust impairs vasomotor responses to both endothelium-dependent and -independent vasodilators at 6 hours. On the basis of this initial study, it is unclear whether the impairment is primarily mediated by the vascular endothelium or is a result of smooth muscle dysfunction. However, reduced NO bioavailability in the presence of increased systemic or vascular oxidative stress is an attractive hypothesis.

The endothelium is a major target of oxidative stress, and this interaction plays an important role in the pathophysiology of vascular disease.[20] Superoxide radicals, produced as a consequence of oxidative stress, combine with NO to form peroxynitrite, thus reducing NO bioavailability in the vessel wall and shifting the balance toward vasoconstriction. In vascular smooth muscle cells, superoxide inhibits the activity of enzymes such as soluble guanylyl cyclase[21] and cGMP-dependent protein kinase,[22] thereby reducing both endothelium-dependent and -independent NO-mediated vasodilation.

We hypothesized that our initial findings were due to the oxidative effects of diesel exhaust, and as such, vascular impairment would occur early. In the subsequent study, we have demonstrated an acute impairment to endothelium-dependent and -independent vasodilators, but we were also
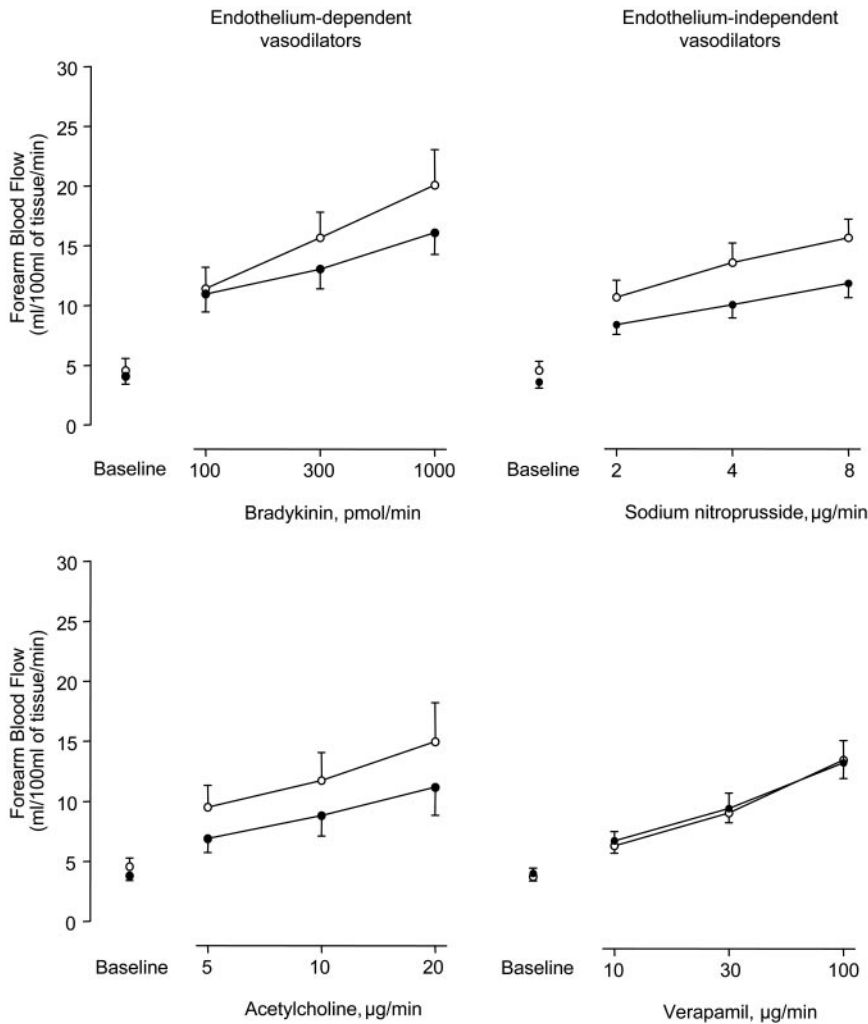
Figure 1. Infused FBF in subjects 2 to 4 hours after diesel exposure (●) and air (○) during intrabrachial infusion of bradykinin, acetylcholine, sodium nitroprusside, and verapamil. For all dose responses, $P<0.0001$. For diesel exposure (●) vs air (○), bradykinin $P<0.05$, acetylcholine $P<0.05$, sodium nitroprusside $P<0.001$, and verapamil $P=$NS.

able to show that vasodilation to the calcium channel antagonist verapamil was unaffected. This suggests that the mechanism of vascular dysfunction involves increased consumption of NO, whether it be endogenously derived from endothelial NO synthase or from an exogenous source, such as sodium nitroprusside. Indeed, in vitro studies provide support for this mechanism, with Ikeda et al[23] demonstrating that incubation of aortic ring preparations with diesel exhaust particles resulted in a dose-dependent inhibition of acetylcholine-mediated relaxation, an effect abolished by coincubation with superoxide dismutase.

Our findings of an acute effect of exposure to air pollution are consistent with recent epidemiological studies that report a significant increase in risk of acute myocardial infarction as little as 2 hours after exposure to road traffic[8] or an increase in $PM_{2.5}$.[1] Our studies add to those of Brook et al,[24] who demonstrated a reduction in brachial artery diameter immediately after exposure to a mixture of concentrated ambient particles and ozone. In contrast, they did not find an effect on endothelium-dependent or -independent vasodilation by flow-mediated and nitroglycerine-induced dilation. This may reflect differences in the potency of the pollution models used or the technique used to assess vascular function. Exposures to concentrated ambient particulates are inherently variable in

magnitude and composition, whereas in our study, each volunteer received a standard exposure to combustion-derived particulates of known toxicity. Alternatively, it is possible that the vascular effects of particulate matter are mediated primarily in the resistance vessels, as assessed by plethysmography, rather than in the conduit arteries, as assessed by ultrasound of the brachial artery.

Fibrinolytic Function

Acute endogenous t-PA release from the endothelium regulates the dissolution of intravascular thrombus and is a critical determinant of cardiovascular outcome. This is exemplified by the clinical observation that in ≈30% of patients with acute myocardial infarction, spontaneous reperfusion occurs within 12 hours of vessel occlusion. The increased risk of atherothrombosis and myocardial infarction in cigarette smokers is at least in part explained by impaired fibrinolytic capacity.[10,11]

We have described an impairment in acute endogenous fibrinolytic capacity after diesel exhaust inhalation. This abnormality may have prothrombotic consequences that could plausibly result in acute cardiovascular events.[8] t-PA release was reduced 6 hours after exposure but not at the earlier time point, suggesting that this impairment is mediated by an inducible pathway or a change in protein synthesis.
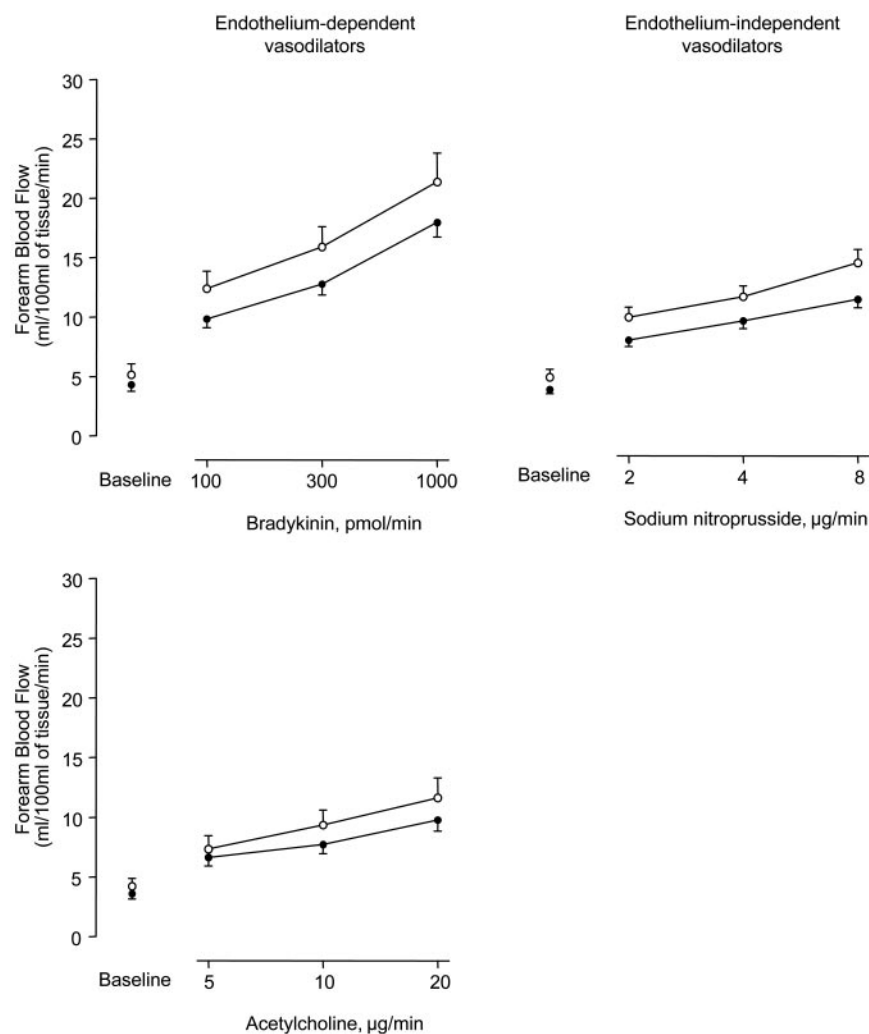
Figure 2. Infused FBF in subjects 6 to 8 hours after diesel exposure (●) and air (○) during intrabrachial infusion of bradykinin, acetylcholine, and sodium nitroprusside. For all dose responses, $P<0.0001$. For diesel exposure (●) vs air (○), bradykinin $P<0.05$, acetylcholine $P=0.07$, and sodium nitroprusside $P<0.001$.

Indeed, culture of human umbilical vein endothelial cells with particulate matter for 6 hours inhibits both the synthesis and release of t-PA in a dose-dependent manner.[25] Given that cigarette smoking and air pollution share common toxicological properties, the present findings are consistent with previous observations in the peripheral[10] and coronary[11] circulations of cigarette smokers and suggest a potential common etiologic factor.

TABLE 3.   Plasma t-PA Antigen Concentrations After Air and Diesel Exposure

	Air (Bradykinin, pmol/min)				Diesel (Bradykinin, pmol/min)			
	0	100	300	1000	0	100	300	1000
2 Hours								
tPA antigen, ng/mL								
Noninfused arm	7.0±0.6	7.0±0.7	7.7±0.8	9.4±1.2	7.2±0.8	7.5±0.8	8.0±0.8	8.9±0.8
Infused arm	6.5±0.5	8.8±1.4	12.2±1.9	17.1±1.3*	6.6±0.7	9.8±1.5	13.7±0.9	18.7±2.7*
Difference	−0.5±0.3	1.7±0.8	4.6±1.2	9.3±1.1*	−0.3±0.4	2.2±0.8	5.3±1.4	9.9±2.2*
Net t-PA release, ng/100 mL of tissue per min	−3.3±2.2	6.6±2.7	27.3±4.3	81.3±10.7*	−0.2±1.0	8.9±3.0	29.4±6.1	82.9±17.8*
6 Hours								
tPA antigen, ng/mL								
Noninfused arm	5.8±0.5	7.1±1.1	7.0±0.6	7.7±0.6	5.5±0.6	5.6±0.5	5.7±0.4	7.1±0.5
Infused arm	6.0±0.5	9.6±1.7	12.0±1.3	18.6±2.5*	5.3±0.6	7.4±0.9	10.0±1.0	14.5±1.3*‡
Difference	0.2±0.2	2.6±1.7	5.4±1.1	11.7±2.5*	−0.2±0.2	2.0±0.6	4.6±0.8	8.0±1.1*†
Net t-PA release, ng/100 mL of tissue per min	0.7±0.9	15.8±9.4	42.9±7.3	138.2±27.8*	−1.0±0.5	10.6±2.9	33.2±5.1	82.5±11.5*†

Values are reported as mean±SEM.
ANOVA (dose response), *$P<0.0001$; ANOVA (air vs diesel), †$P<0.05$, ‡$P<0.001$.
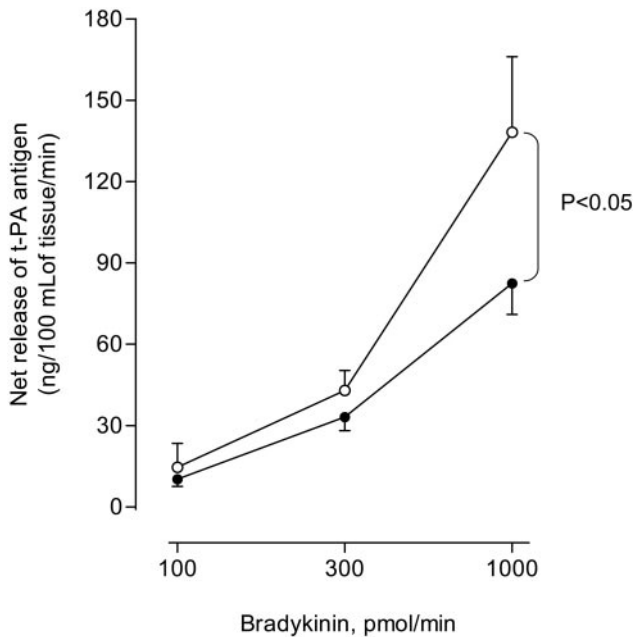
Figure 3. Net release of t-PA antigen in subjects 6 hours after diesel exposure (●) and air (○) during intrabrachial infusion of bradykinin. For both dose responses, $P<0.0001$. For diesel exposure (●) vs air (○), $P<0.05$.

Air Pollution, Oxidative Stress, and Inflammation

A substantial body of evidence supports a role for oxidative stress in determining the toxicity of ambient pollution[26] and in the proinflammatory effects of diesel exhaust particles.[27,28] Reactive oxidant species arise not only from the redox potential of the pollutants themselves but also from the activation of alveolar epithelial cells or resident macrophage and the recruitment of circulating neutrophils.

The potential for inhaled nanoparticulate air pollution to cause local inflammation is not in doubt, and airway neutrophilia has been demonstrated in a healthy volunteer study with the same concentration of diesel particulate and exposure system.[15] In our study, inhaled diesel exhaust was not associated with an increase in blood leukocytes, plasma IL-6 and TNF-α, or serum CRP concentrations, but this does not rule out the influence of other circulating inflammatory factors, oxidized lipids, or proteins.

Population Risk and Exposure

As an important source of combustion-derived particulate, diesel exhaust is strongly implicated in the observed adverse effects of air pollution.[4,29,30] Particulate matter concentrations can regularly reach levels of 300 μg/m^3 in heavy traffic, occupational settings, and the world's largest cities.[31] Exposure to 300 μg/m^3 for 1 hour increases a person's average exposure during a 24-hour period by only 12 μg/m^3. Changes of this magnitude occur on a daily basis in even the least polluted of cities and are associated with increases in cardiorespiratory mortality.[3] Our model is therefore relevant in both the composition and magnitude of exposure for the assessment of short-term health effects in humans.

Diesel exhaust is a complex mixture of gases and particles, and from our findings, we cannot exclude a nonparticulate cause of the adverse vascular effects. However, in epidemiological studies, particulate matter has been held responsible for the majority of the adverse health effects of air pollution.[32] Ambient NO$_2$ can be considered a surrogate for traffic-derived pollution,[29] but it has little adverse effect in controlled chamber studies, even at the exposure levels seen here.[33] There are no reports of the potential adverse cardiovascular effects of toxins such as hydrocarbons or formaldehyde. We therefore suggest that the vascular effects described herein are mediated primarily by diesel exhaust particulates and not its other components, but this needs to be more definitively addressed.

Conclusions

Exposure to increased levels of combustion-derived air pollution for as little as 1 hour can impair vasomotor function and endogenous fibrinolysis in humans. We provide evidence that this may be the result of reduced NO bioavailability in the vasculature and postulate that this effect is mediated by oxidative stress induced by the nanoparticulate fraction of diesel exhaust. These data provide a plausible mechanistic link to explain the association between air pollution and acute myocardial infarction.

Disclosures

None.

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CLINICAL PERSPECTIVE

Air pollution is a serious problem in the world's major cities owing to the combustion of fossil fuels such as diesel oil. In particular, there has been recent interest in the consistent association between increased levels of air pollution and cardiovascular morbidity and mortality. The World Health Organization estimates that a quarter of the world's population is exposed to unhealthy concentrations of air pollutants. The American Heart Association recently issued a scientific statement highlighting the increased cardiovascular risk associated with exposure to air pollution and emphasized the importance of establishing a mechanistic link to explain these epidemiological observations. We have previously demonstrated vascular dysfunction in cigarette smokers. Because combustion products and particulate matter are common to both polluted air and cigarette smoke, we hypothesized that air pollution would cause detrimental vascular effects. This is the first study to demonstrate that inhalation of diesel exhaust, a common urban air pollutant, can impair vascular function in humans. Using a double-blind, randomized, cross-over study design, we have assessed the effects of diesel exhaust inhalation on 2 important and complementary aspects of vascular function: the regulation of vascular tone and endogenous fibrinolysis. We were able to demonstrate that both are impaired and plausibly related to the well-documented adverse cardiovascular effects of air pollution. These important findings provide a plausible mechanism that links air pollution to the pathogenesis of atherothrombosis and acute myocardial infarction.